Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material

   [X] a sequence listing

   [ ] table(s) related to the sequence listing

   b. format of material

   [X] on paper

   [ ] in electronic form

   c. time of filing/furnishing

   [X] contained in the international application as filed

   [ ] filed together with the international application in electronic form

   [ ] furnished subsequently to this Authority for the purposes of search and/or examination

   [ ] received by this Authority as an amendment* on

2. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of Box V:

The common general knowledge of the art is that gastric distension contributes to feelings of satiety and the PSA would appreciate that agents that affect gastric distension would be useful in the treatment of conditions that involve unusual appetites, for example, obesity. The specification at pages 47 and 48 describes known mechanoreceptors known to be involved in gastric distension. Therefore the PSA would investigate the role of ligands to these receptors in the modulation of satiety and be led to the invention as presently defined in claims 1-17 and 32-35. Therefore the subject matter of these claims is obvious and does not meet the requirements of Article 33(3) PCT with regard to inventive step.

Industrial Applicability (IA) Claims 1-17 and 32-35

The invention defined in the claims is considered to meet the requirements of Industrial Applicability under Article 33(4) of the PCT because it can be made by, or used in, industry.

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CLAIMS

1. A method for modulating the perception of satiety in a subject, said method comprising administering to said subject an effective amount of an agent selected from the list consisting of:

(i) an agent which is an agonist of a mechanoreceptor selected from the list consisting of ENAC, βENAC, γENAC, ACCN3, ACCN4, ASIC1, ASIC2, ASIC3, ASIC4, BLINAC/hiNaC (ACCN5), TREK1, TREK2, TRAAK (KCNK4), SCNN1C, KCNK2, TRPM1, TRPM2, TRPM3, TRPM4, TRPM6, TRPM7, TRPM8, TRPC1, TRPC2, TRPC3, TRPC4, TRPC6, TRPV2, TRPV3, TRPV6 and TRPM8;

(ii) an agent which is an antagonist of a mechanoreceptor list in (i);

(iii) an agent which inhibits expression of a gene encoding a mechanoreceptor listed in (i); and

(iv) an agent which enhances expression of a gene encoding a mechanoreceptor listed in (i);

wherein increasing or decreasing the level of or activity of the mechanoreceptors changes the perception of satiety in said subject.

2. The method of Claim 1 wherein the mechanoreceptors are selected from the list consisting of TRPV2, ACCN5, TRPM1, TRPM4, TRPV6 and TRPV4.

3. The method of Claim 2 wherein the mechanoreceptor is TRPV2.

4. The method of Claim 1 or 2 or 3 wherein the agent is an agonist of the mechanoreceptor which promotes the perception of satiety.

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5. The method of Claim 1 or 2 or 3 wherein the agent is an antagonist of the mechanoreceptor which reduces the perception of satiety.

6. The method of Claim 1 wherein the subject is a mammal.

7. The method of Claim 6 wherein the mammal is a primate.

8. The method of Claim 7 wherein the mammal is a human.

9. The method of Claim 6 wherein the mammal is a laboratory test animal.

10. The method of Claim 5 wherein the agent is an antagonist of TRPV2 selected from the list consisting of 1-[β-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl]-1H-imidazole, ruthenium red dye and salts, homologs, orthologs, analogs, isomers, enantiomers, derivatives and functional equivalents thereof.

11. The method of Claim 10 wherein the agent is a ruthenium red dye selected from the list consisting of ruthenium (6t), tetradecaaminedi-m-oxotrihexachloride or a trans (8Cl) isomer or an enantiomer thereof, and an ammoniated ruthenium oxychloride or a steroisomer or enantiomer thereof.

12. A pharmaceutical composition when used to modulate the perception of satiety in a subject comprising an agent selected from the list consisting of:

(i) an agent which is an agonist of a mechanoreceptor selected from the list consisting of ENAC, βENAC, γENAC, ACCN3, ACCN4, ASIC1, ASIC2, ASIC3, ASIC4, BLINAC/hiNaC (ACCN5), TREK1, TREK2, TRAAK (KCNK4), SCNN1C, KCNK2, TRPM1, TRPM2, TRPM3, TRPM4, TRPM6, TRPM7, TRPM8, TRPC1, TRPC2, TRPC3, TRPC4, TRPC6, TRPV2, TRPV3, TRPV6 and TRPM8;

(ii) an agent which is an antagonist of a mechanoreceptor list in (i);

(iii) an agent which inhibits expression of a gene encoding a mechanoreceptor listed in (i); and

(iv) an agent enhance expression of a gene encoding a mechanoreceptor listed in (i);

and one or more pharmaceutically acceptable carriers and/or diluents.

13. The pharmaceutical composition of Claim 12 wherein the agent is an antagonist of TRPV2 selected from the list consisting of 1-[β-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl]-1H-imidazole, ruthenium red dye and salts, homologs, orthologs, analogs, isomers, enantiomers, derivatives and functional equivalents thereof.

14. The pharmaceutical composition of Claim 12 wherein the agent is a ruthenium red dye selected from the list consisting of ruthenium (6t), tetradecaaminedi-m-oxotrihexachloride or a trans (8Cl) isomer or an enantiomer thereof, and an ammoniated ruthenium oxychloride or a steroisomer or enantiomer thereof.

15. Use of an agent selected from the list consisting of:

(i) an agent which is an agonist of a mechanoreceptor selected from the list consisting of ENAC, βENAC, γENAC, ACCN3, ACCN4, ASIC1, ASIC2, ASIC3, ASIC4, BLINAC/hiNaC (ACCN5), TREK1, TREK2, TRAAK (KCNK4), SCNN1C, KCNK2, TRPM1, TRPM2, TRPM3, TRPM4, TRPM6, TRPM7, TRPM8, TRPC1, TRPC2, TRPC3, TRPC4, TRPC6, TRPV2, TRPV3, TRPV6 and TRPM8;

(ii) an agent which is an antagonist of a mechanoreceptor list in (i);

(iii) an agent which inhibits expression of a gene encoding a mechanoreceptor listed in (i); and

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(iv) an agent enhance expression of a gene encoding a mechanoreceptor listed in (i);

in the manufacture of a medicament for the control of obesity.

16. Use of Claim 15 wherein the agent is an antagonist of TRPV2 selected from the list consisting of 1-[β-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl]-1H-imidazole, ruthenium red dye and salts, homologs, orthologs, analogs, isomers, enantiomers, derivatives and functional equivalents thereof.

17. Use of Claim 15 wherein the agent is a ruthenium red dye selected from the list consisting of ruthenium (6t), tetradecaaminedi-m-oxotrihexachloride or a trans (8Cl) isomer or an enantiomer thereof, and an ammoniated ruthenium oxychloride or a steroisomer or enantiomer thereof.

18. A method for treating or preventing symptoms of obesity, anorexia, need of satiation, weight maintenance conditions, metabolic energy levels and/or inflammatory disease conditions in an animal said method comprising administering to said animal an effective amount of a compound selected from a calcium uptake inhibitor or promoter, a blocker or promoter of TRPV2 calcium channels and a biological dye which inhibits or promotes calcium uptake for a time and under conditions to ameliorate one or more symptoms.

19. The method of Claim 18 wherein the compound is selected from 1-[β-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl]-1H-imidazole, a ruthenium red dye and salt, homolog, ortholog, analog, isomer, enantiomer, derivative or functional equivalent thereof.

20. The method of Claim 19 wherein the compound is 1-[β-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl]-1H-imidazole and a ruthenium red dye or a salt or isomer or enantiomer thereof.

21. The method of Claim 19 wherein the compound is a ruthenium red dye or a salt or isomer or enantiomer thereof.

22. The method of Claim 18 or 19 or 20 or 21 wherein the animal is a mammal.

23. The method of Claim 22 wherein the mammal is a human.

24. The method of Claim 18 wherein the compounds modulate calcium ion uptake in cells of the stomach wall.

25. The method of Claim 24 wherein the cells are neuronal cells of the myenteric plexus.

26. Use of a compound selected from a blocker or promoter of TRPV2 calcium channels, a biological dye which inhibits or promotes calcium uptake of salts, homologs, orthologs, analogs, isomers, derivatives or functional equivalents thereof to modulate *inter alia* obesity, anorexia, satiation, weight maintenance, metabolic energy levels and/or inflammatory disease conditions in a subject in the manufacture of a medicament for the treatment of symptoms associated with obesity, anorexia, need for satiation, metabolic energy levels and/or inflammatory disease conditions.

27. Use of Claim 26 the compound is selected from 1-[β-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl]-1H-imidazole a ruthenium red dye and salt, homolog, ortholog, analog, isomer, enantiomer,derivative or functional equivalent thereof.

28. Use of Claim 27 wherein the compound is 1-[β-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl]-1H-imidazole and a ruthenium red dye or a salt or isomer or enantiomer thereof.

29. Use of Claim 27 wherein the compound is a ruthenium red dye or a salt or isomer enantiomer thereof.

30. Use of Claim 26 wherein the disease is obesity itself or various manifestations such as diabetes and disorders associated with imbalances in metabolic energy levels are disease and disorders associated with genetic disorders.

31. The method of Claim 18 or use of Claim 26 wherein the inflammatory condition is acne, angina, arthritis, aspiration pneumonia, empyema, gastroenteritis, inflammation, intestinal flu, necrotizing enterocolitis, pelvic inflammatory disease, pharyngitis, pleurisy, raw throat, rubor, sore throat, stomach flu and urinary tract infections, Chronic Inflammatory Demyelinating Polyneuropathy, Chronic Inflammatory Demyelinating Polyradiculoneuropathy, Chronic Inflammatory Demyelinating Polyneuropathy and Chronic Inflammatory Demyelinating Polyradiculoneuropathy.

32. A pharmaceutical composition when used for treating or controlling obesity, anorexia, satiation, weight maintenance, metabolic energy levels and inflammatory conditions comprising a compound selected from a calcium uptake inhibitor or promoter, a blocker or promoter of TRPV2 calcium channels and a biological dye which inhibits or promotes calcium uptake for a time and under conditions to ameliorate one or more symptoms and one or more pharmaceutically acceptable carriers and/or diluents.

33. The pharmaceutical composition of Claim 32 wherein the compound is selected from 1-[β-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl]-1H-imidazole a ruthenium red dye and salt, homolog, ortholog, analog, isomer, enantiomer, derivative or functional equivalent thereof.

34. The pharmaceutical composition of Claim 33 wherein the compound is 1-[β-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl]-1H-imidazole and a ruthenium red dye or a salt or isomer or enantiomer thereof.

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35. The pharmaceutical composition of Claim 34 wherein the compound is a ruthenium red dye or a salt or isomer or enantiomer thereof.